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The Wesley M. Carpenter Lecture

THE INFLUENCE OF THE DIENCEPHALON AND HYPOPHYSIS UPON GENERAL AUTONOMIC FUNCTION*

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It is a graceful tribute to the memory of Wesley M. Carpenter that the President of the Academy of Medicine should make the lectureship which perpetuates his name a part of the Annual Graduate Fortnightly series. For Carpenter as an officer in many medical societies gave unfailing and distinguished service to the cause of medical education.

The honour of giving a Carpenter Lecture is as much appreciated by me as it is undeserved. With the flattering invitation from the Academy of Medicine to prepare this teaching lecture came the stern injunction that I was to speak plainly, in simple language—and yet the subject proposed is neither plain nor simple; a subject which at present is firing the imagination of physiologist and chemist, of prophet and of charlatan.

Hidden away in the mysterious hollow of the sella turcica lies a miracle-working gland whose reputed performances would have brought a blush of shame to the swarthy cheek of Aladdin. He never thought of trying to produce acceleration of growth, of sex function, of metabolism and of water drinking, or of suddenly inhibiting these processes. It did not occur to him that by rubbing up one side of his lamp he might summon an increased

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sugar tolerance, and by rubbing down the other side diabetes mellitus.

But this pituitary "lamp of Aladdin" as it hangs at the bottom of the infundibulum is not an isolated organ like other glands. Its posterior lobe is continuous with the infundibulum and with the diencephalon, that part of the brain which surrounds the third ventricle and includes potent autonomic centers. These centers, unobserved and unsuspected, have always regulated the vital processes of the body through peripheral sympathetic and parasympathetic pathways. Far from being isolated from the diencephalon we now find that the hypophysis is connected with it by a portal circulation of veins and we now suspect further that certain chemical principles distilled within the hypophysis may pass directly through the nervous tissue and into the third ventricle, there to bathe the paraventricular centers.

The most obvious pathological condition of the anterior lobe is neoplastic change and examples of these neoplasms will serve most easily to recall certain of the functions normally discharged by this doughty little gland. The mother cells or chromophobe cells of the anterior lobe differentiate into acidophilic and into basophilic cells and correspondingly tumors of three types have been described, i.e. chromophobe, acidophilic (or eosinophilic) and basophilic adenomas.

Clinical Hypopituitarism

The most frequently encountered tumor of the pituitary is the chromophobe adenoma. In my opinion the cells of this tumor are not identical in appearance with the true mother cells of the anterior lobe. They differ morphologically but we need not tarry to quarrel with terminology. At all events these tumors seem to produce no hormone of themselves but by their slow expansion within the sella turcica they gradually destroy the hypophysis just as a craniopharyngeal pouch epithelioma may do from without the sella.

The resultant symptoms of this destruction are usually first gonadal. If the patient be a woman menses cease perhaps years before other signs appear. Sexual activity in the male is interfered with at a later stage. Experimental

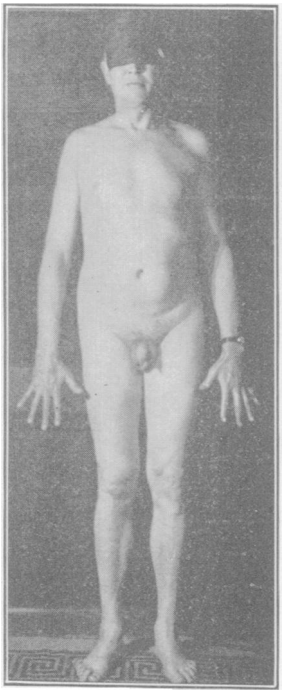

Fig. 1. Case of chromophobe adenoma of pituitary with decrease in secondary sexual characteristics.

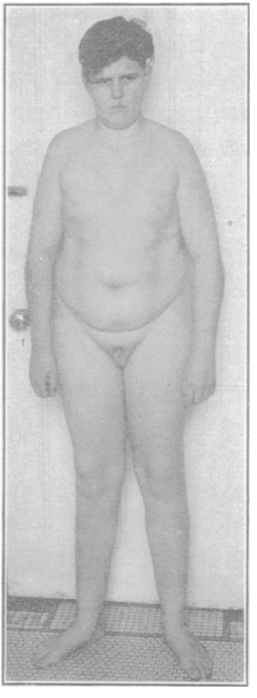

Fig. 2. Example of hypopituitarism in a boy of 17 years. Adiposogenital dystrophy of Fröhlich. (Kindness of Medical Department, Royal Victoria Hospital.)

hypophysectomy in animals results also of course in suppression of the oestral cycle and in atrophy of testicular germinal epithelium.

Hypopituitarism (Fig. 1) is thus best seen in such cases of partial destruction of the hypophysis manifested by decrease or disappearance of secondary sex characteristics, a pasty complexion and appearance of fat; this with decreased basal metabolism and arterial hypotension

related no doubt to the atrophy of thyreoid and of adrenal cortex demonstrable at post mortem examination.

Hypopituitarism in childhood (Fig. 2) produces the adiposogenital dystrophy of Fröhlich (1901) which was really first described by Babinski (1901).

Clinical Hyperpituitarism

Chromophile or acidophilic adenomas on the other hand evidently elaborate a substance capable of producing the growth changes familiar to all students of medicine as acromegaly. When such tumors begin before maturity typical acromegalic giants are produced. If they make their appearance later (Fig. 3) this caricature of growth

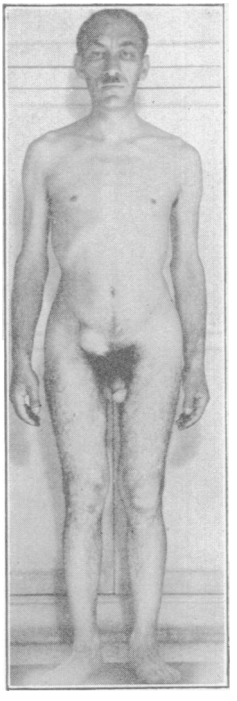

Fig. 3. Case of acidophilic adenoma of pituitary producing acromegalic changes in an adult. Picture taken two years after transfrontal removal of the tumor which resulted in an astonishing reduction in the manifestations of acromegaly. The secondary sex characteristics may be contrasted with Figures 1 and 2.

is superimposed upon an adult frame. The presence of these acidophilic cells is apparently invariable in the tumors associated with acromegaly. This fact may cast some light upon the acidophilic cells of the functioning gland.

Hypophysectomy in immature animals arrests growth almost immediately. That growth is really controlled by the anterior lobe is further borne out by the fact that a purified growth hormone has been isolated from the anterior lobe by Collip, Selye and Thompson (1933) and by Evans and his co-workers (1933). Furthermore, Evans points out that administration of this principle, if pushed after closure of epiphyseal lines, is capable of producing acromegaly in dogs, as previously shown by Putnam and Teel (1929).

The third type of adenoma is less easily assessed for its true value at the present time, i.e. basophil adenoma described by Cushing (1932).

These adenomas which are usually small produce their effect, according to Cushing, in part directly by migration of adenomatous basophilic cells into the parasympathetic centers in the vicinity of the third ventricle and in part through the local circulatory pathways. The neurotropic effect is said by him to be adiposity, hypertension and late vascular hypertensive changes. The patients (Fig. 4) have an over development of secondary sexual characteristics, become hirsute and show striations in the skin from rapid addition of subcutaneous fat.

Pituitary basophilism may be (and has been) confused with hyperadrenalism leading in several cases to exploration of the adrenal glands and indeed adenomas of the adrenal cortex have been encountered. It is not possible at the present time to make the assumption that the similar basophil cells of the pituitary concern themselves principally with the elaboration of a sex hormone or with the activation of parasympathetic mechanisms. Nevertheless, Cushing has called attention to a most important

Fig. 4. Case of verified basophilic adenoma of the pituitary; kindness of Dr. Cushing, pictured by him as the Kraus-Raab case.

group of cases in which there is evidently a polyglandular disturbance of which the initiating factor may well be the basophil adenoma.

But neoplastic cells usually differ from normal cells in activity as in growth and, in general, tumors of the pituitary are prone to produce a kaleidoscopic effect upon patients. This may be due to over-secretion of certain cells followed by under-secretion when the neoplastic compression increases. And this explains the findings of "fugitive acromegaly", of transient diabetes mellitus, of fleeting hyperthyroidism, of acromegalic giants who show late tendency to "adiposogenital dystrophy".

Another explanation of the fugitive endocrine phenomena may be found in the fact that injection of pituitary extracts sometimes seem to build up a resistance so that

the end result of such injection may be an effect opposite to the one desired.

Clinical Apituitarism

Epitheliomas of the craniopharyngeal pouch most often produce hypopituitarism with adiposogenital dystrophy early in life as they press down into the sella turcica gradually destroying its contents (Fig 2). These tumors may go further to complete destruction of the gland resulting in hypopituitary dwarfism of childhood, and in the pitiful emaciated adult sufferers from so-called Simmonds' disease (Fig. 5A-5B). Experimental hypophysectomy fully bears out the findings of clinical hypopituitarism and Smith has described a cachexia resembling that of Simmond's disease produced by experimental hypophysectomy.

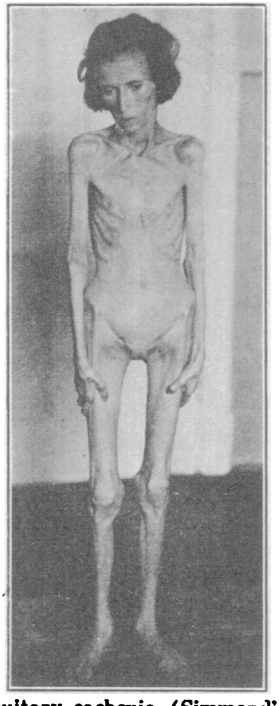

Fig. 5A. Case of pituitary cachexia (Simmond's disease) due to tumor shown in Figure 5B. It was considered that she represented complete apituitarism but at necropsy a very small flattened remnant of the hypophysis was still present.

Anterior Pituitary Extracts

A clearer picture of the activity of the anterior pituitary lobe [perhaps a little too clear!] is emerging from the studies of the biochemists who have now isolated (1) a thyreotropic principle and (2) an adenotropic extract.

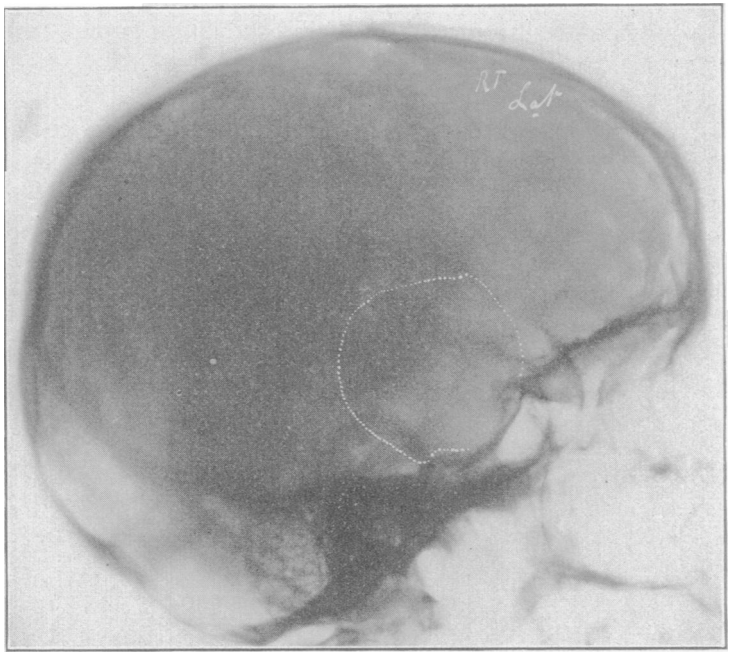

Fig. 5B. Same case as Figure 5A. The dotted outline indicates the partially calcified capsule of a craniopharyngeal epithelioma.

In substantiation of this some clinical evidence is also at hand that over-activity of the pituitary is associated with hyperplasia of the thyreoid and of the cortex of the adrenal, and conversely that hypopituitarism is associated with atrophy of these glands. The increased metabolism usually associated with an active chromophile adenoma of acromegaly has as its probable cause increased activity of the thyreoid while the low basal metabolism and low blood pressure of hypopituitarism may well have deficient activity of thyreoid and adrenal as their immediate cause.

Biochemists have further isolated (3) a growth extract, (4) a lactogenic hormone, (5) a gonadotropic element and (6) possibly a diabetogenic principle.

These elements express most clearly the multiform activity of the normal functioning anterior lobe but their separation does not necessarily indicate the existence of such hormones circulating in the blood. Collip (1933) suggests that the number of true hormones in the gland is very limited, that in the process of extraction certain active groups are released from "a master protein molecule". Clinicians, he concludes, will have to use not one, but various combinations of these active substances as indicated in the particular case.

Professor Collip evidently does not dream how deeply rooted in the hearts of what we may call the *adenotropic* clinicians was the practice of administering, not one, but many extracts long before true extracts existed.

DIENCEPHALON

The diencephalon* (called also interbrain or tween brain) surrounding as it does the third ventricle and including thalamus, hypothalamus and infundibulum is a very old portion of the brain being well developed in the lowest vertebrate forms which possess little or no forebrain. Without daring to stop for a detailed anatomical discussion I may point out only that lying beneath the walls of the third ventricle are the supra-optic nuclei and the nuclei of the tuber cinereum (Fig. 6—S and T) which seem to be closely associated with the posterior lobe of the pituitary being connected with each other by afferent and efferent fibers.

This complex Beattie (1932) has labelled the anterior mechanism. He might perhaps have borrowed from Cushing the term "neurohypophyseal" mechanism. There

* Excellent analyses of autonomic representation within the brain have been provided by Greving (1928), by Huber and Crosby (1928) and most recently by Beattie (1932) and Josephy (1932).

is some evidence that this anterior group of nuclei may deserve the adjective parasympathetic because of the relationship of the tuberal nuclei to the craniosacral division of the autonomic nervous system with its peripheral control through vagus and pelvic nerves.

The posterior group of nuclei (P, Fig. 6) located in the walls of the posterior portion of the third ventricle above the corpora mammillaria are said to contain the sympathetic centers. Efferent tracts composed of short neurones which pass downward through brain stem and

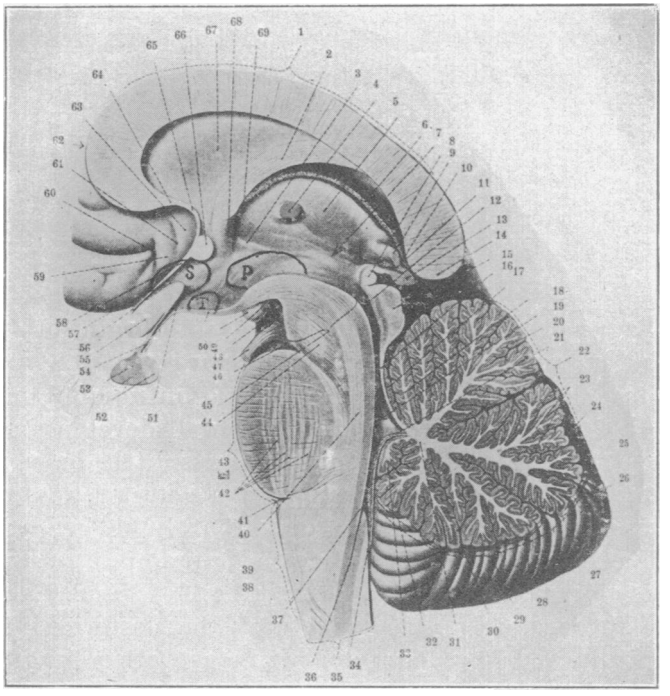

Fig. 6. Diencephalon after Sobotta. S=supra-optic nuclei; T=tuberal nuclei; P=posterior hypothalamic nuclei as indicated by Beattie.

cord are assumed for both anterior and posterior complexes. But in the case of the posterior group a sympathetic pathway was actually followed by Beattie, Brow and Long (1930) from this region down the posterior longi-

tudinal bundle and cervical cord, through second, third and fourth thoracic anterior roots to the stellate ganglion and thence to the heart.

The afferent tracts so far demonstrated to these centers are chiefly derived from diencephalon and from forebrain. It seems somewhat surprising that the afferent pathways should come from "headward" regions. It may be that forebrain and thalamus form stations on the pathway from periphery to hypothalamic centers. But it is also evident that what may be considered afferent impulses reach these centers through the blood stream. For example, if the blood entering the thalamus be raised above the normal temperature there is a response from the nervous mechanism in the vicinity which results in a discharge chiefly parasympathetic which lowers the general temperature by sweating, vasodilatation and diminished oxidation.

Attention must be called also to the existence of a portal system of veins which pass upward from both anterior and posterior lobes of the hypophysis through the infundibulum (Popa and Fielding, 1932, see also Basir, 1932) where they break up into a secondary distributing net beneath the infundibular recess of the third ventricle. Further, a colloid substance has been described in these veins by Collin (1928), (also by Popa and Fielding, 1932 and by Cushing, 1933). This finding makes it evident that much of the hormonal material from the pituitary may act directly upon the nervous system and in particular upon the so-called parasympathetic centers of the diencephalon. There is, however, a partial drainage into the general circulation by way of the cavernous sinus which is derived chiefly from the sinusoids in the anterior lobe. Innervation of the posterior lobe is by nerve fibers from the supra-optic and tuber nuclei while the anterior lobe is innervated by fibers derived from the carotid plexus (Dandy).

In January, 1928 I was fortunate enough to have under my care at the Presbyterian Hospital in this city a patient with a small, discrete, encapsulated tumor so placed that it impinged upon the anterior and superior portion of the

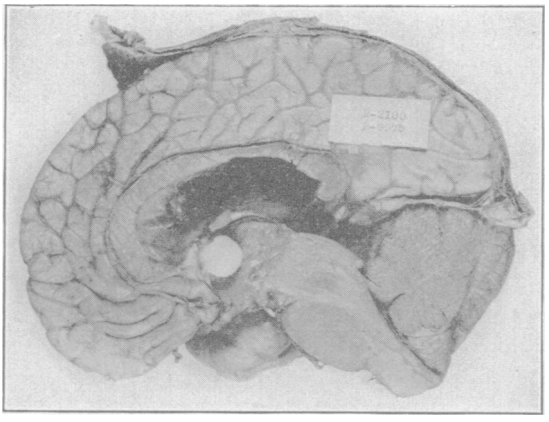

Fig. 7. Encapsulated tumor compressing anterior portion of thalamus of both sides and causing diencephalic autonomic epilepsy (from Penfield, 1929).

thalamus of each side, as shown in Figure 7. She was subject to recurring seizures which resembled epileptic attacks excepting that the manifestations of the attack were confined to the realm of the autonomic nervous system. The case was published under the heading Diencephalic Autonomic Epilepsy.

An epileptic discharge is a gross revelation of the function of an area, somewhat in caricature no doubt, but the true features of function are there to be scanned (Jackson, 1931) by him who can read as Hughlings Jackson did. The epileptic phenomena which I shall recount in order of their habitual appearance may therefore reveal to us the function of this region. We may think of the disturbance spreading downward and backward from the tumor site.

1. Prodromal restlessness and sometimes a desire to void.
2. Sudden intense vaso-dilatation of skin of face, arms and breasts.
   Sudden rise in blood pressure from 110 up to 200.
3. Lacrimation.
   Diaphoresis.
   Salivation.

Dilatation (or contraction) of pupils.
Protrusion of eyes (not invariably present).
Increase of rate and of pressure of pulse.
Marked retardation of respiratory rate.
(Elicitability of pilomotor reflex).

4. Disappearance of superficial blush and fall of blood pressure, slowing and weakening of pulse.
5. Hiccoughs (from 3-5 in number).
6. Transient shivering.

During the present year I have had under my care at the Royal Victoria Hospital three other cases who showed certain features of autonomic epilepsy. One of these may be mentioned here; a woman of 29 with a tumor involving the under surface of the left temporal lobe and extending to midbrain and thalamus. She had recurring slight attacks consisting of sudden headache followed by yawning and hiccoughing and sometimes associated with patchy erythema in different areas of the body.

There was one attack of greater severity characterized by a rise of blood pressure to 200 over 90 whereas the usual level approximated 100 over 70. With this there was a simultaneous rise of pulse rate to 130, flushing and appearance of irregular erythema over chest and thighs, spontaneous appearance of goose flesh, slowing of respirations to 4 per minute, salivation, lacrimation, dilatation of left pupil and contraction of right.

This description tallies sufficiently with the first to make it clear that we are not dealing with a discharge of a parasympathetic system alone as Cushing concludes in reviewing the first case (1932-a p. 84). It is an explosive indiscriminating discharge which betrays the spacial relationships both of parasympathetic and sympathetic function. The dilatation of peripheral vessels and sweating might be considered as parasympathetic in nature but the pilomotor response and increased pulse rate, increased blood pressure and protrusion of eyes obviously belong in the sphere of the sympathetic.

Another instance may be cited. In the case of a boy of 14 I approached a tumor of the third ventricle through the right lateral ventricle under nupercaine analgesia. Taking hold of the tumor as it presented in the foramen of Monro I moved it within the third ventricle. The patient "hummed" and then vomited in a projectile manner, after which there was generalized shivering followed by sudden frantic scratching of the inner aspect of the left thigh and there appeared very marked reddening of that skin area.* Following this he became disoriented as to place. His temperature rose from 99° at the time of the shivering to 102° an hour and a half later. It is recognized that the urticarias and the general reaction, for example after serum injection, do not occur if the patient is anaesthetized. It may well be that such reactions proceed from the autonomic centers.

The conclusion to be drawn is that there is probably represented in the diencephalon blood pressure control, heart rate control, vascular dilatation, sweating, salivation, lacrimation, control of respiration, pilomotor reactions, shivering, hiccoughing and yawning and perhaps micturition.

Experimental physiologists have timidly pushed localization of autonomic function upward from spinal cord and bulb to mesencephalon until finally they also have burst into the diencephalon with enthusiastic abandon. Some of their results may be described below.

Cardiovascular. From the posterior portion of the hypothalamus a control is exerted over cardiac acceleration and the secretion of epinephrin through the sympathetic nerves. This was demonstrated in a negative fashion by Beattie, Brow and Long (1930) by experimental incisions. From stimulation of the tuber nuclei further forward

* Next morning the patient's skin was scratched with great vigor for four minutes. There appeared no reddening of the skin comparable to that just described. It is evident that the erythema was not simply secondary to the scratching.

Beattie (1932, a) secured slowing of the heart and this effect he was able to abolish by vagus section.

Gastrointestinal. Experimental lesions in an indefinitely localized region of the hypothalamus, have been shown to be followed by ulceration and fatal perforation of the wall of the stomach or duodenum (Keller, 1932). Clinically it is interesting that Rokitansky years ago demanded a routine examination of the base of the brain in all autopsies where "softening" or ulceration of the stomach was found. And numerous workers have recognized the neurogenic element in the causation of ulcer. But this has not been localized strictly to the hypothalamus by clinicians.

For example a student of 22 years was operated upon by my associate, Dr. William Cone, and a medulloblastoma removed from the cerebellum and roof of the fourth ventricle. Six days later he died from haemorrhage in a duodenal ulcer. There were two smaller ulcers near by. Excepting that he had vomited twice before operation there was nothing in the history to suggest that an ulcer was present before operation. Following operation which was quite uneventful he vomited blood at intervals until death and necropsy showed the ulcers to be recent.

Cushing has reported three cases of perforation of oesophagus, stomach or duodenum in patients suffering from cerebellar tumor, and Blackfan (1933) oesophageal perforation associated with a case of occlusion of the aqueduct of Sylvius and in three cases of meningitis. Beattie (1932, b) stimulated electrically the region of the infundibulum producing in the exposed stomach increased peristalsis, increased secretion and after half an hour of continued stimulation small hyperaemic patches upon the mucous membrane of the lesser curvature.

But all this work must be interpreted carefully, as gastrointestinal ulceration has been reported to follow stimulation of the vagus and of various parts of the brain. Furthermore, hyperperistalsis has been known to follow stimulation of certain areas of the cerebral cortex ever

since the work of Bochefontaine in 1876. And Watts and Fulton* inform me that intussusception follows excision of the pre-motor cortex in the monkey concluding that this region exerts an inhibitory influence upon peristalsis. The removal of this area seems to permit focal ringlike intestinal contractions to form which tend to produce intussusception. Whether the center that is released may be the diencephalic parasympathetic centers of Cushing and of Beattie is open to conjecture.

Finally Cushing has observed in man that intraventricular injection of pituitrin or of pilocarpine both of which, he assumes, act upon the paraventricular parasympathetic centers selectively, produced an effect upon the stomach characterized by hypertonicity, hypermotility and hyperchlorhydria in addition to diaphoresis and fall in body temperature.

Temperature control. It is a fact familiar to all physiologists that the decerebrate animal whose brain has been removed down to the anterior end of the midbrain has lost ability to control its temperature and if its life is to be preserved elaborate thermostatic regulation is necessary (Bazett and Penfield, 1922). As the result of a bout of running movements or for some other reason the temperature may rise uncontrollably and the animal be destroyed as though, in a way, it had been the subject of spontaneous internal combustion. Unilateral decerebration at the usual Sherringtonian level mentioned above does not destroy the control mechanism as I have kept such a cat for over six months and it controlled its temperature quite well even through the vicissitudes of an English winter. Further, if in addition to the midbrain the major portion of the diencephalon be left intact as in Goltz's dog, temperature control is preserved.

Within the hypothalamic area are situated the circuits which discharge this most important function automatically and every neurosurgeon knows to his sorrow that to

* Personal communication.

disturb a tumor in this region may arouse that "bête noir" of hyperthermia which results in death within a day or two. Such a death is preceded by steadily rising temperature with peripheral vasoconstriction, rising pulse and rising respiratory rate—a syndrome called hyperthermia for want of a better name. It seems to be an acute disorder of the mechanisms which ordinarily preserve an even temperature.

Sleep "that knits up the ravelled sleeve of care" has hidden itself away from scientific exploration. Hess (1932) has recently tried to surprise it within the diencephalon. He points out that in profound sleep the deep reflexes are absent, carbon dioxide is increased in the blood stream to a level which would stimulate the respiratory center of a waking individual. Food assimilation is increased, heart rate slowed, body temperature reduced. In other words, he urges, there exists during sleep a parasympathetic dominance. Further evidence of this dominance is the fact that in sleep the pupil becomes contracted. This contraction gives way to dilatation, paradoxically enough, when the sleeper is awakened even though it be done by shining a light into his eyes.

Zondek and Bier (1932) claim that a sleep producing bromine compound (bromhormone) is formed by the pituitary gland which empties itself of this beneficient substance during sleep. The result of this emptying is said to be that an increased amount of the material may be detected in the medulla oblongata at that time.

In an attempt to prove his theory of parasympathetic dominance in sleep Hess selected a drug, ergotamine (Sandoz), which inhibits the sympathetic system peripherally and activates the parasympathetic. This he injected into the third ventricle. The result was apparent sleep with pupillary contraction. This contraction gave way to dilatation under the influence of light as in the case of true sleep. He then went one step further. Placing a very small enamelled steel bipolar electrode in the brain and allowing the animal to recover from the operation, he

found by using a pulsating direct current that he could put the animal to sleep. But this effect could be produced not from a small "sleep center" but from a series of areas distributed through the extra-pyramidal motor system. Sleep, he concludes, is at all events a positive phenomenon arising deep within the brain.

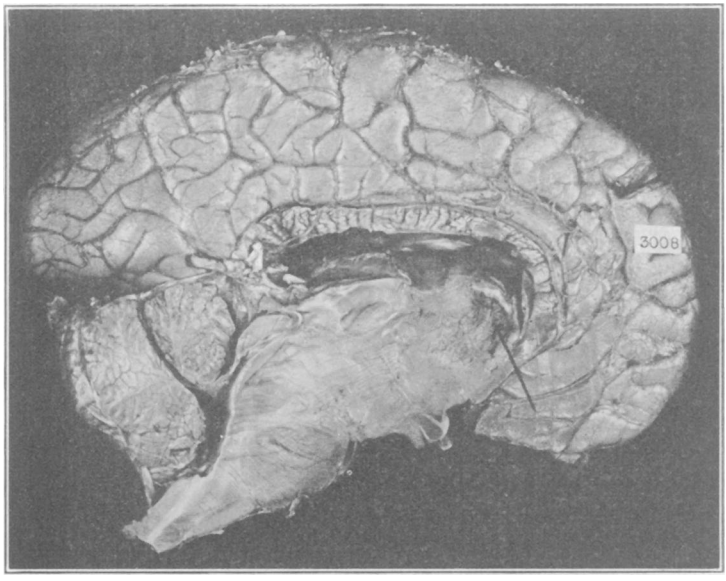

Fig. 8A. Tumor in anterior portion of thalamus producing "unconquerable sleep."

From a clinical point of view much work has accumulated upon narcolepsy. I will ignore this literature but refer to a patient* who for eighteen months before his death suffered from an "unconquerable tendency to fall asleep". He was the chauffeur of one of my associates! There was little else in the history and we saw the poor fellow repeatedly. He would fall asleep during a conversation. Figures 8A and 8B show the site of his tumor.

* This case will be reported in detail by my associate, Dr. William Cone.

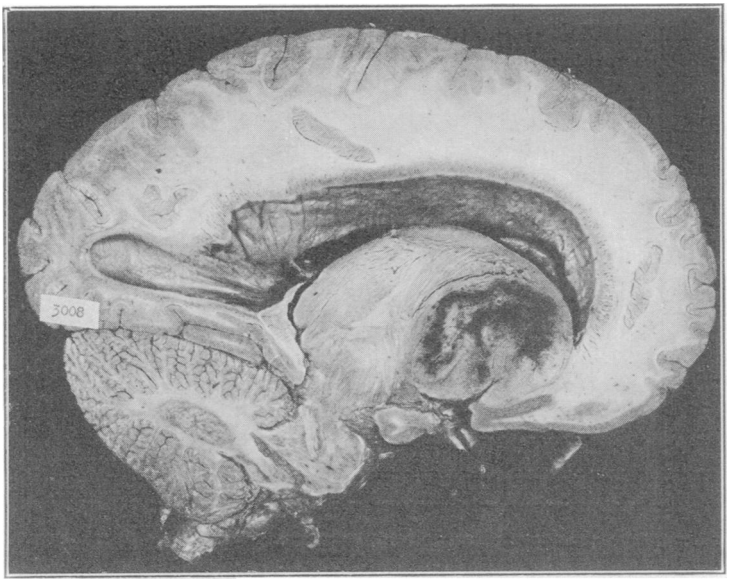

Fig. 8B. Same tumor as 8A at deeper level to show circumscribed character.

Lesions of this sort do not give rise to chronic irritation and, unless there are epileptic seizures, the effect of such a tumor can only be paralytic. In this case one may assume that the tumor in the anterior portion of the thalamus has released the sleep mechanism below it from a normally inhibitory control.

Water Balance. The condition known as diabetes insipidus is characterized by polydipsia and polyuria. This condition may be produced by lesions of the tuber cinereum when the hypophysis is left intact as shown by Bailey and Bremer (1921), (also Camus and Roussy, 1922). Clinically it is encountered most often as the result of a suprasellar tumor. The condition can be controlled almost at once by injections of posterior lobe extract which is a further evidence of the interaction of the pituitary and the paraventricular nuclei.

It was first suggested by Herring (1908) on histological grounds that secretion from the pars intermedia and from

the posterior lobe might reach the ventricle by passage through the infundibulum, and Lucien (1909) suggested that the basophilic cells which are found in the posterior lobe and infundibulum all the way to the ventricle were actually cells which had migrated upward from the "adenohypophysis."

Numerous workers have found in fluid from the cisterna magna (but not in lumbar fluid) an oxytocic substance which increases contraction of excised uterus as pituitrin would do (Karplus and Peczenik, 1930). Further a substance is found in the fluid which causes melanophore cells in the frog's skin to expand so that the skin becomes darker. Karplus and Peczenik found that direct stimulation of the hypothalamus served to increase this oxytocic substance which they believed to be pituitrin. This increase takes place even after sympathetic nerves are cut.*

The suggestion comes to mind, of course, that a lesion situated in the tuber because of its position forms a block to the upward passage of a pituitrin-like substance. But we are in the end left with no certain knowledge except that diabetes insipidus is produced not by an intrasellar lesion but by a suprasellar one, while the specific therapeutic agent, i.e. pituitrin or one of its derivatives, can be made not from tuberal tissue but from the posterior lobe of the hypophysis.

Carbohydrate metabolism. In 1858 Claude Bernard was seeking to find in the vagus nucleus a nervous mechanism that had to do with glycogen formation when he first punctured the floor of the fourth ventricle. He was surprised to find that it produced transient glycosuria. This puncture of Claude Bernard was the earliest proof that diabetes might be dependent upon a disorder of the central nervous system. It has since been shown by Aschner that puncture higher up in the hypothalamus would also produce

* It must be added that van Dyke and Bailey believe the oxytocic substance to be in fact only an increase of calcium within the fluid. They found this increase both in lumbar and cistern fluid, however.

glycosuria. It is, further, common knowledge that a severe emotional upset can give rise to transient glycosuria and that anaesthesia may have the same result.

Tumors of the nervous system if situated near the third ventricle may be associated with diabetes mellitus as in the carefully studied case of Byrom and Russell (1932). Van Bogaert reported two cases of tumor involving the infundibulum in which there was hyperglycaemia without glycosuria.

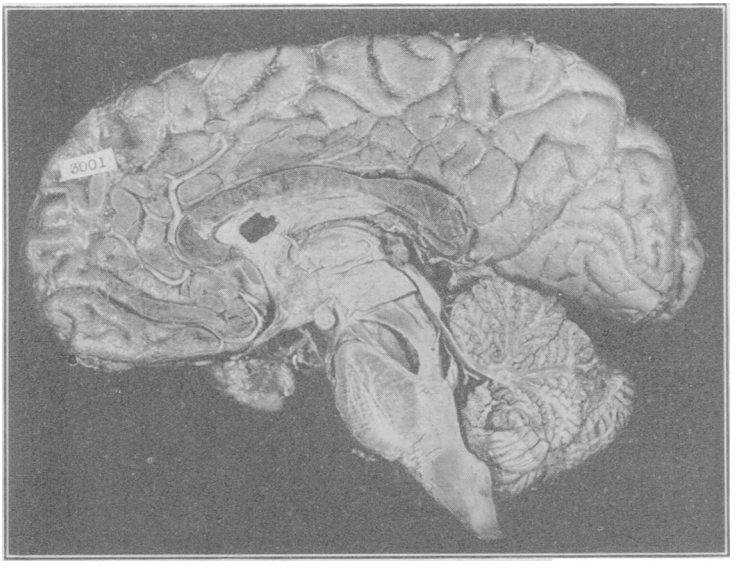

Fig. 9. Case of diabetes mellitus with cyst in midbrain; kindness of Medical Department, Royal Victoria Hospital.

I may also mention a most interesting case* of diabetes mellitus of five years' standing in which Dr. E. H. Mason found that insulin had little effect in curbing the glycosuria. Autopsy showed in addition to degeneration of the pancreas the cyst of the midbrain shown in figure 9. A lesion in the vicinity of the descending autonomic pathways was actually suspected before death.

* To be published fully by Dr. E. H. Mason.

But even more significant of a higher control is the oft reported association of diabetes mellitus with acromegaly (25 per cent of cases according to Davidoff and Cushing). The diabetes which is thus produced is not progressive and may disappear. The acidophilic adenoma of acromegaly seems to produce a sort of hyperpituitarism. The diabetes mellitus which may result might well be the result of the presence of an excess of some pituitary product.

On the other hand tumors of other types which compress the pituitary and adjacent ganglia tend to produce hypopituitarism and may be associated only with increased sugar tolerance. Such a patient can, of course, ingest over 100 grams of glucose without the glycosuria which would appear in the normal subject.

The explanation offered is that the pituitary and its associated hypothalamic nuclei exert normally an inhibitory influence upon the islets of Langerhans or upon insulin itself so that a defect in this inhibitory action renders more insulin available and therefore gives to the patient an increased glucose tolerance.

In experimental hypophysectomy dogs show a normal blood sugar level but if they are starved sudden hypoglycaemic crises are apt to occur which may be fatal. Similar severe hypoglycaemia in clinical hypopituitarism has been reported by Wilder (1930). Furthermore, hypophysectomized dogs are hypersensitive to insulin (Houssay and Magenta, 1929) which might be expected if the removal of hypophysis had also removed an inhibitory influence upon insulin.

Additional evidence which points in the same direction is the recent demonstration from the Argentine School (this time Houssay and Biasotti, 1931) that hypophysectomy decreases the severity of diabetes so that dogs after complete pancreatectomy may survive six months whereas controls with normal hypophyses died in one to four weeks with severe diabetes. Thus hypophysectomy may yet be proposed to some unsuspecting neurosurgeon as a cure for diabetes mellitus.

In toads pancreatectomy produces very severe diabetes. If the pituitary or even only the anterior glandular portion be removed pancreatectomy has little effect. But if now anterior lobe be implanted beneath the skin, next day an intense diabetes with glycosuria and hyperglycaemia occurs and finally Houssay (1932) has produced the same effect by injection of anterior lobe extract. Barnes (1933) has verified this work and obtained the diabetogenic effect with both the growth and the thyreotropic fractions derived from anterior lobe.

The inhibitory action of anterior lobe upon insulin seems established but it has not been shown yet whether it acts through the general blood stream or whether its effect is directly exerted upon the diencephalon which may in turn exert the inhibitory action upon the pancreas through the vagus. There is in fact evidence which favors the vagus as the final common diabetogenic pathway.

Finally it may be suggested that possibly the control of the liberation of the diabetogenic principle from the pituitary may be found to lie in the diencephalon itself. In this diabetogenic activity may lie an explanation of some of the discrepancies that exist between the clinical findings of diabetes mellitus and the pathological state of the pancreas at autopsy.

Certain principles are emerging from the obscurity that has cloaked the diencephalon and hypophysis and the internist may now lift his eyes to the nervous mechanisms which unsuspected have always co-ordinated the vital processes and preserved the internal environment.

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